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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/732,862	12/10/2003	Katelynne Lyons	LOR-136.0 (9720/88881)	9117

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EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/732,862	LYONS ET AL.	
	Examiner	Art Unit	
	BO PENG	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This Office Action is in response to the amendment filed April 29, 2008. Claims 1-47 are pending and considered in this Office action.

Double Patenting

2. (**Prior rejection-maintained**) The rejection of Claims 1-46 under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over (1) Claims 1-78 of 09/930,915; (2) Claims 1-53 of 10/787,734; (3) Claims 98-109 of 10/805,913; (4) Claims 79-115 of 10/806,006, (5) Claims 47-85 of 11/508,655, **is maintained**.

3. Applicant acknowledges the rejection and does not wish to prematurely respond.

Claim Rejections – 35 USC § 112-Scope of enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. (**Prior rejection-maintained**) The rejection of Claims 1-47 under 35 U.S.C. 112, first paragraph for failing to comply with the enablement requirement (scope of enablement**) is maintained** for the reasons of record.

In response to Applicant's argument:

6. Applicant argues that the specification enables any person skilled in the art to make the claimed HBc chimers containing up to about 5% substituted amino acids residues in the HBc

SEQ ID NO: 1 because the specification teaches various substitutions in page 73-75 and Figure 1. It is submitted that those substitutions are more than a sufficient number to constitute "about 5 percent".

7. Applicant's argument is not convincing. The scope of the claims encompasses a large number of HBc chimers that contain 5% substitutions variously arranged along the sequence of SEQ ID No: 1. As a result, the claims encompass a large number of alleged HBc chimers with no defined structure. Claims 25-26 further require that the claimed HBc particle has an enhanced satiability comparing to wt HBc. The specification indicates: "More preferably, about 9 residues are different from the ayw sequence (SEQ ID NO: 1) at residue positions 2-183, and most preferably about 5 residues are different in shorter sequences, e.g., 2-149, or 2-156, or 2-163 are proportional to those discussed before based on percentage" (Para 2, p. 75). However, the specification has not shown that such alleged HBc chimers containing 5% substitutions variously arranged along the sequence of SEQ ID No: 1 can still form viral-like particles like HBc, nor would the resultant HBc particles necessarily have enhanced satiability as claimed. As discussed in the previous Office actions, a single amino acid can create problems resulting from changes in conformation that can't be adequately predicted in advance. See Rudinger, J. at page 6 (Cited in the previous Office action).

8. Thus, based on the disclosure in the application, and on the knowledge in the art, those skilled in the art would not be able to make the alleged stabilized HBc chimers containing 5% substituted amino acid residues in the HBc SEQ ID NO: 1

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. (**Prior rejection-maintained**) The rejection of Claims 1-6, 8-14, 16-28, 30-42 and 46 under 35 U.S.C. 103(a), as being unpatentable over Pumpens, in view of Zlotnick and Zhang, **is maintained** for the reasons of record.

In response to Applicant's argument 1:

11. Applicant provided following arguments in Remarks p. 20 regarding the teaching of Zlotnick:

> The Action first discusses the alleged contribution of the Zlotnick manuscript. The premise that Zlotnick teaches the *C*-terminal cysteine can stabilize an HBc chimer molecule as recited in the claims here cannot be agreed with. This premise is inconsistent with the statements and data provided therein by Zlotnick.
>
> For example, Zlotnick explicitly states: "[p]urified Cp*149 and Cp*150 assemble into capsids under the same conditions as other constructs, with or without DTT. These capsids were *indistinguishable* (emphasis added) by negative staining electron microscopy and sedimentation on sucrose gradients." (See page 9558, column I, paragraph 1, Results and Discussion section.) As a second example, Zlotnick reports: "[a]t a resolution of ~20A, the outer surface of the Aull- labeled [monomaleimidyl-undecagold-labeled] Cp*150 capsid is indistinguishable (emphasis added) from those of unlabeled Cp147 and Cp183 capsids, (cf. Fig. 4 Top)." (See page 9558, column 2, and paragraph 1) These facts would lead one skilled in the art to conclude that *C*-terminal cysteines are not important for HBcA capsid formation or stability.
>
> The Zheng manuscript echoes this conclusion. For example, Zheng states: "[e]ach of the cysteines of HBcAg has been eliminated both singly and in combination. All the proteins were shown to have very similar physical and immunochemical properties. All assemble into essentially identical core particle structures. Therefore, disulfide bonds are not essential for core particle formation." (see page 9422, Abstract). It is believed that these statements alone are strong evidence to refute the Action's proposal that Zlotnick teaches that *C*-terminal cysteine can stabilize HBcA particles.

12. Applicant's citations of Zlotnick are not complete, and the conclusion is misleading. The following is the complete citation of Zlotnick from page 9558, column 1, paragraphs 1 and 2, Results and Discussion section):

> [P]urified Cp*149 and Cp*150 assemble into capsids under the same conditions as other Cp constructs (10, 15), with or without DTT. These capsids were indistinguishable by negative

staining electron microscopy and sedimentation on sucrose gradients (data not shown). When reduced CP*150 capsids were stored without DTT for 2 days, >90% of the protein oxidized to form disulfide-bonded dimers (Fig. 2 *a*). These bonds stabilize the quaternary structure of the capsid, as attested by the observation that oxidized Cp*150 capsids—unlike CP*149 capsids or reduced Cp*150 capsids—are resistant to dissociation by 3.5 M urea (Fig. 2 *b*). Knowledge of the location of residue 150 (see below) indicates that this disulfide bond links two dimers (Fig. 1 *b*) and is distinct from the intradimeric disulfide observed in Cp proteins with native cysteines (16, 25).

Generally, when Cp proteins are stored in a low ionic strength, high pH buffer they do not polymerize (10). However, when stored in this buffer without DTT, Cp*150 dimers assemble into capsids, as determined by negative stain electron microscopy and analytical ultracentrifugation. A high proportion of the protein in these capsids is disulfide-bonded (Fig. 2 *a*). These data show that disulfide bond formation by Cp*150 can promote capsid assembly. Without disulfide formation, higher-order structures do not accumulate in storage buffer, i.e., the rate for dissociation is greater than the rate of association. Formation of these disulfide bonds stabilizes complexes against dissociation. Thus, under these conditions, Cp polymerization appears to involve an equilibrium between subunits, assembly intermediates, and capsids (36). We also note that, in capsids, the cysteine 150 residues from adjacent subunits must be close enough to one another to form a covalent bond, a distance of 4.6–7.4 Å between α carbons (37). (Underline emphasis added by the examiner)

13. In view of teachings recited above, one skilled in the art would conclude that Zlotnick explicitly teaches that Cp*150, which contains a *C*-terminus cysteine, is more stable than Cp*149, which does not contain a *C*-terminus cycteine. These facts would lead one skilled in the art to conclude that *C*-terminal cysteines are important for HBcA capsid formation and stability.

14. Zhang teaches that Cys48 and Cys107 are not essential for formation of an interchain disulfide bond with another monomer because mutations at Cys48 and Cys107 do not affect formation of HBc dimer particles. Zhang illustrates that mutation(s) at Cys48 and/or Cys107 result in only HBc dimers, rather than a mixture of dimers and monomers (Para 2, right col. p. 9424, and Figure 3).

15. In view of the combined teachings of Zlotnick and Zhang, one of ordinary skill in the art would be motivated to modify native Cys48 and Cys107 of HBc and add a Cys at the HBc *C*-

terminus in order to obtain more stable and uniform HBc dimers.

In response to Applicant's argument 2:

16. Applicant asserts from Figure 2a of Zlotnick that the polyacrylamide gel shown therein depicts disulfide bonded *dimers* **not HBcA core protein capsid particles**. Those capsids are the entities recited in the claims to have enhanced stability. (Remarks Para 2, p. 21) Applicant argues that nothing in Zlotnick has shown the capsids behave like dimers, See Remarks p22-23. Applicant asserts "The present claims recite the stability of the particles assembled from those monomers and dimers. As such, a disclosure concerning the stability or lack thereof of dimers or monomers neither teaches nor suggests anything of relevance to the claimed subject matter whether taken alone or with any other disclosure" (Remarks, Para 4, p. 21).

17. This argument is not convincing because while targeting Zlotnick Fig. 2 alone, Applicant again ignores the teachings in Zlotnick specifically related to **HBcA core protein capsid particles.** Specifically, Zlotnick shows capsid protein in Figure 2(b). Zlotnick teaches in Fig. 2(b) as recite: "(b) size exclusion chromatography of **capsid** protein (particles) after exposure to 3.5 M urea. Samples are oxidized Cp*150 (solid line), Cp*150 with 130 mMDTT (dashed line) and Cp*149 (dotted line)". See Description of Fig. 2, right col. p. 9557. Here, oxidized Cp*150 is polymerized capsid, Cp*150 with 130 mM DTT is reduced Cp*150, containing both polymerized and disassociated capsid particles. Thus, Figure 2b simply shows that Cp*150, shown as single peak of capsid polymer, is more stable than Cp*149, shown as two peaks of polymerized and disassociated capsid.

18. Moreover, In Figure 3, Zlotnick teaches cryo-election microscopy of Cp149, Cp*150 capsid. In Figure 4, Zolonick shows image reconstruction of T = 4 HBV capsids. In Fig. 1b, Zlotnick teaches Cp150 dimers connected by a disulfide bond between Cys-150 residues (See e.g. 1b, Description of Fig. 1b, and page 9558, col. 1, paragraphs 1 and 2, Results and Discussion section). These figures clearly show that Cp*150 forms capsid particles assembled from HBc

dimers!

In response to Applicant's argument 3:

19. Applicant again argues that the instant specification teaches the absence of one, or both Cys 48 and Cys 107 can enhance the storage ability of a particle that is otherwise stabilized by the presence of an N- or C-terminal cysteine or both. Applicant asserts that it is a notable difference between the present application and the Zlotnick, Zheng, and Pumpens manuscripts (Remarks, p. 24).

20. Again, this argument is not persuasive. As discussed in the previous Office action, Zhang shows that a single mutation at Cys48 produced only dimers with no detectable monomers (Figure 3, lane 3), and mutations at both Cys48 and Cys107 results in only dimers (Para 3, right col. and also see Figure 3, lane 7). Thus, Zhang teaches that removal of Cys48 or/and Cys107 results in unified HBc dimers. It is known that dimer HBc is basic unit to form HBc particle. Thus, Given the knowledge that Cys48 and Cys107 are not essential for native core particle formation as taught by Zhang, given the knowledge that removal of native Cys48 and Cys107 results in only HBc dimers as taught by Zhang, and also given the knowledge that HBcΔ with C-terminal Cys is more stable than HBcΔ without C-terminal Cys, one of ordinary skill in the art is capable to correctly apply such knowledge to the design of an HBcΔ chimer, and would have created the alleged HBcΔ chimer containing Cys at its C-termini and substituted amino acids at Cys48 and Cys107. In other words, the claimed invention is a "predictable use of prior art elements according to their established functions." KSR, page 13. In view of the teachings of Zlotnick and Zhang, one of ordinary skill in the art would recognize that the teaching of the

instant specification cited above is consistent with teachings of Zlotnick and Zhang.

21. Applicant further asserts that Cp150, which is HBc containing C-terminus Cys, failed to associate into dimmer or has readily disassociated as shown in Zlotnick's Fig. 2a lane 6 and lane 7 (Remarks, p. 25), suggesting Cp150 is not stable. (Remarks p. 25 and 26)

22. This argument is not relevant to the claims. Applicant argues the limitations that are not in the claims. The instant claims are directed to a genus of HBc protein molecule up to about 600 amino acid residues in length,…(ii) self-assembling into particles. The claims encompass HBc monomers, dimers and polymers up to about 600 amino acids. The instant claims do not require being absence of HBc monomer. Zlotnick shows in Fig. 2a that the vast majority of Cp150, which contains no C-terminus Cys, is polymers (See lanes 6 and 7), while Cp149, which contains no C-terminus Cys, is monomers (See lane 5). Thus, Zlotnick shows that Cp150 is a polymerized HBc molecule, which meets the claim limitation.

23. Furthermore, Fig. 2b shows that Cp*150, shown as single peak of HBc polymer capsid, is more stable than Cp*149, shown as two peaks of polymerized and disassociated capsid. Thus, Zolotnick has demonstrated that C-terminus-Cys enhances stability of HBc.

24. (**Prior rejection-maintained**) The rejection of Claims 1-6, 8-28, and 30-46 under 35 U.S.C. 103(a), as being unpatentable over Page and Birkett, both in view of Zhang, **is maintained** for the reasons of record.

In response to Applicant's argument:

25. Applicant again argues that none of the disclosures teach that the removal of cysteines at

positions 48 and 107 of the chimer molecules would enhance the stability of the subsequently formed capsid, and none of them teaches or suggests that the addition of a terminal cysteine to such a capsid results in added stability as well.

26. As indicated in the previous Office actions, Page teaches "[t]he removal of the arginine repeats residues the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a disulphide bond which in the native structure is important for the formation of a stable particle." (See page 2). Also see Para 26, the Office action dated November, 17, 2006. Zhang shows that HBc mutants that lack Cys at either position 48 or 107 yield stable dimers, without detectable monomers (See Figure 3, lane 3 and lane 7). In view these teachings, one of ordinary skill in the art would apply such knowledge to make a chimer HBc without Cys 48 and 107, while retaining the *C*-terminal cysteines, in order to achieve more stabile HBcΔ particles. Therefore, the invention as a whole is obvious to one of ordinary skill in the art, in view of the prior art.

Remarks

27. No claim is allowed. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph. D. can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Bo Peng/
Patent Examiner
July 19, 2008

/Zachariah Lucas/
Primary Examiner, Art Unit 1648